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10/789,169	02/27/2004	Daniel R. Weinberger	NIH222.001C1	9926
20995 7590 03/21/2007 KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614			EXAMINER SITTON, JEHANNE SOUAYA	
			ART UNIT	PAPER NUMBER
			1634	
SHORTENED STATUTORY PERIOD OF RESPONSE		NOTIFICATION DATE		DELIVERY MODE
3 MONTHS		03/21/2007		ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

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**Office Action Summary**

Application No.

10/789,169

Applicant(s)

WEINBERGER ET AL.

Examiner

Jehanne S. Sitton

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4,5,7,8,10,11,13,14,16,17,19,20,22,23 and 25-51 is/are pending in the application.
- 4a) Of the above claim(s) 25-51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, and 22-23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)         | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Currently, claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, 22-23, and 25-51 are pending in the instant application. Claims 25-51 are withdrawn from consideration as being drawn to non elected inventions. Claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, and 22-23 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. This application contains claims 25-51 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The rejection under 35 USC 102(e) over Sklar II is moot in view of the amendments to the claims.

5. The rejection of claims 1,4,7, and 10 under 35 USC 103(a) is withdrawn in view of the In re Katz declaration filed with the response.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2, 5, 8, 11, 14, 17, 20, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims have been amended to recite "...verbal memory, assayed with memory scores...". This recitation is indefinite as the use of the term "score" is unclear. It is not clear if the term is meant to be directed to a measurement of a memory task, or whether it is a particular type of memory task.

8. Claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

The claims have been amended to recite "will not have impaired hippocampal function [dependent memory].... The response asserts that the claims have been amended to conform to US Patent 6,458,541. This statement is not understood, the cases are unrelated. The response asserts that support for the amendment can be found throughout the specification and at para 0008. The specification has been thoroughly reviewed, however the specification does not set forth methods for predicting the likelihood that a human will not have impaired hippocampal

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function or hippocampal verbal memory by detecting a G to A single nucleotide polymorphism which results in the met allele at amino acid position 66 of BDNF. The specification sets forth methods for predicting impaired or enhanced hippocampal function or verbal memory, however the specification does not appear to provide support for this recitation. Notably, Bath teaches (Bath and Lee, Cognitive, Affective & Behavioral Neuroscience, 2006, vol. 6, pages 79-85) that the effect of the met66val polymorphism is different in various ethnicities (page 81, col 2, last para). Accordingly, it does not appear that the presence of the val allele would be necessarily indicative that a human “will not have” impaired hippocampal function or verbal memory.

Additionally, the amendment to recite “hippocampal dependent verbal memory” does not appear to be supported by the specification. At para 0008, the specification asserts that in cohorts, “the met allele had abnormal patterns of hippocampal activation while performing memory tasks”, however the specification is silent as to which memory tasks were administered and it is not clear that the effect of the met allele on verbal memory was ‘hippocampal dependent’. Accordingly, the amendments appear to have introduced new matter into the claimed invention.

9. Claims 1-2, 4-5, 7-8, 10-11, 13-14, 16-17, 19-20, 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements

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and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

The claims (1 and 2) are drawn to a method of predicting the likelihood that a human will have impaired or will not have impaired hippocampal function assayed with fMRI or impaired hippocampal dependent verbal memory, assayed with memory scores, by obtaining a DNA sample and determining the presence or absence of a single nucleotide polymorphism (SNP) G to A resulting in the substitution of a methionine for a valine (G=Val, A=Met) at amino acid position 66 relative to the start of the precursor protein sequence in BDNF, wherein the presence of a G to A polymorphism resulting in a methionine residue at position 66 is indicative of the likelihood that the human will have impaired hippocampal function, assayed with fMRI, or impaired hippocampal dependent verbal memory, assayed with memory scores, and wherein the presence of an A to G resulting in a valine residue at position 66 is indicative of the likelihood that the human will not have impaired hippocampal function, assayed with fMRI, or impaired hippocampal dependent verbal memory, assayed with memory scores. The claims (13 and 14) are also drawn to a method of predicting the likelihood that a human will or will not have impaired hippocampal function, assayed with fMRI, or impaired hippocampal dependent verbal memory, assayed with memory scores by obtaining a biological sample containing the precursor

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BDNF protein or relevant portion thereof and determining the amino acid present at position 66 relative to the first amino acid of the precursor protein wherein the presence of a methionine residue at position 66 is indicative of the likelihood that the human will have impaired hippocampal function, assayed with fMRI, or impaired hippocampal dependent verbal memory, assayed with memory scores, and wherein the presence of a valine residue at position 66 is indicative of the likelihood that the human will not have impaired hippocampal function, assayed with fMRI, or impaired hippocampal dependent verbal memory, assayed with memory scores.

The claims are further limited to humans that are at risk for development of impaired hippocampal function, or impaired hippocampal dependent verbal (claims 4-5, 16, 17). The claims are also further limited to individuals that exhibit clinical symptomology associated with (claims 7-8, 19-20) or individuals that are clinically diagnosed as having (claims 10-11, 22-23) impaired hippocampal function, or impaired hippocampal verbal memory.

The nature of the invention, therefore, requires the knowledge of a predictive association between the presence of an A/met or G/val at codon position 66 of BDNF and impaired or enhanced hippocampal function, impaired hippocampal dependent verbal memory.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that BDNF is a neurotrophin and contains at least one known nonconservative SNP producing a met66val substitution (page 3). The specification teaches that verbal memory was assessed in 184 patients with schizophrenia, 283 siblings, and 101 controls and that NAA (N acetyl aspartate) was available for 110 subjects (page 4). The specification teaches that the effect of genotype was significant across all groups for memory scores ( $p < .008$ )

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and that the met allele was associated with poorer performance. However, the specification teaches that BDNF genotype had no effect on IQ or prefrontal cognitive measures.

The specification teaches that the met allele was associated with reduced hippocampal NAA ( $p < .07$ ), however this result does not appear to be statistically significant. The specification further teaches that in two separate cohorts studied with fMRI, subjects with the met allele had abnormal patterns of hippocampal activation while performing memory tasks, compared to val/val homozygote subjects. The specification, however does not teach if this was statistically significant (page 4). Although the specification suggests that the met allele may be associated with impaired hippocampal function or impaired verbal memory, the specification does not provide any guidance or working examples that the val allele alone is predictive of the likelihood that a human will not have impaired verbal memory or impaired hippocampal function. Bath (Bath and Lee, Cognitive, Affective & Behavioural Neuroscience, 2006, vol. 6, pages 79-85) teaches that the effect of the met66val polymorphism is different in various ethnicities (page 81, col 2, last para). Accordingly, it does not appear that the presence of the val allele would be necessarily indicative that a human “will not have” impaired hippocampal function or verbal memory. The specification provides no working examples of human subjects and controls demonstrating that the val allele is associated with enhanced hippocampal function or verbal memory than in normal controls.

The claims encompass analysis in any human individual, which includes any human population. The specification provides no working examples of associations studies between the indicated alleles and different ethnic populations.

The state of the prior art and the predictability or unpredictability of the art:

Although the specification sets forth a number of substantially different hypothesis (page 9, para 0022) the specification does not teach the effect of val66met SNP on BDNF function. The association between the polymorphism and its effect on hippocampal function, verbal memory, and disorders involving impaired memory are unclear. The art at the time the invention was filed, does not make up for the deficiencies in the specification. Association of the met or val allele at codon 66 of BDNF with hippocampal function, verbal memory and disorders involving impaired memory, such as schizophrenia, or Alzheimer's disease (AD), in different populations is highly unpredictable as exemplified by the teachings in the art.

The post filing date art of Neves Pereira (Neves-Pereira et al; Molecular Psychiatry, vol. 10, pages 208-212, 2005) teaches that although the val66met polymorphism has been shown to alter gene function, the risk may depend on the haplotypic background on which the val/met variant is carried (see abstract). As evidenced by the haplotype analysis for SNPs in BDNF, Sklar (Sklar et al; Molecular Psychiatry, vol. 7, pages 579-593, 2002) teaches that 8 BDNF SNPs, including the val66met (a39) polymorphism are found in 6 different haplotypes, which are found at different frequencies in different populations (see table 4). The study of Neves Pereira contradicts the teachings of the specification in that it teaches that the valine allele, as opposed to the methionine allele as disclosed in the instant application, is associated with schizophrenia in a Scottish population (see abstract). Likewise, Kent (Kent et al; Molecular Psychiatry, vol. 10, pages 939-943, 2005) teaches that the valine allele was found to be preferentially transmitted in ADHD (see abstract) and Ventriglia (Ventriglia et al; Molecular Psychiatry, 2002, vol. 7, pages

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136-139) teaches that the homozygosity for the valine allele appears to confer an increased risk for AD (see page 137, first col).

Alternatively, Zhang (Zhang et al; American Journal of Medical Genetics, Part B, vol. 141B, pages 387-393, 2006) teaches that there was no association found for the val66met polymorphism and AD, affective disorders, or schizophrenia. Jonsson (Jonsson et al, Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 30, pages 924-933, 2006) teaches that there were no significantly different allele, genotype, or haplotype frequencies between patients with schizophrenia and controls for the BDNF val66met SNP and teaches that further studies are needed to establish risk with schizophrenia (see abstract). Antilla (Antilla et al; J. Neural Transm, vol. 112, pages 885-890, 2005) teaches that a study by Egan et al, 2003 (applicant's own work) showed that the BDNF G196A polymorphism was not associated with schizophrenia, but that a study by Hong et al 2003 reported that the val/val genotype was slightly more common in schizophrenia patients, at opposite with the teachings of the instant specification. Antilla teaches that in a study of Finnish patients, the G196A (val66met) polymorphism was not associated with risk of schizophrenia, treatment response, or age of onset (see pages 888-889). Further, Antilla teaches that previous studies have suggested that the frequency of val66met polymorphism is different in different ethnic populations. In line with this teaching, the post filing date art of Bath (Bath & Lee, Cognitive, Affective, & Behavioral Neuroscience, vol. 6, pages 79-85, 2006) exemplifies the unpredictability of correlating hippocampal function, verbal memory, or disease risk in different populations, as is broadly encompassed by the claims. Bath teaches that cognitive and behavioral effects associated with the methionine allele have been shown to produce much more robust effects in Caucasians (page

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81, col. 1, 2<sup>nd</sup> full para). Bath teaches that the methionine allele is not uniformly distributed across all ethnicities or all regions of the world and that Northern Europeans appear to be much more affected than Asian populations, despite the fact that a higher proportion of the Asian population carry this allele, suggesting that some ethnicities may compensate for the variation in the BDNF gene through some as yet unidentified mechanism and are thus less affected by the presence of the polymorphism (see para bridging pages 81-82).

The claims (13-14, 16-17, 19-20, 22-23) are also drawn to assessing the precursor protein and determining the amino acid present at position 66, thus encompassing analysis of the BDNF protein (page 6, para 0013), using for example, antibodies that bind to one form of the gene product but not another (page 10, para 0025). However, neither the art nor the specification teach an antibody that is capable of specifically differentiating the BDNF valine66 from the BDNF methionine66 variant. It is unpredictable whether the amino acid change would be sufficient to result in the production of antibodies that can differentiate between the two molecules. In some cases, an antibody elicited by one antigen can cross-react with a different antigen if the two different antigens share an identical or very similar epitope (Goldsby et al., 2003, p. 141). Thus, absent knowledge of the binding epitopes and the effects of the instant polymorphism on those epitopes, it is difficult to predict whether or not any generated antibody will be able to function to differentiate the two alleles in an assay. In the instant case, it is unpredictable as to whether or not an antibody would be able to differentiate between the two variants, a feature that is encompassed by the claimed invention.

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The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

In order to practice the invention as broadly as it is claimed, one would first have to establish that a predictive relationship exists between the val66met polymorphism and impaired hippocampal function, including as assayed by fMRI, or impaired hippocampal dependent verbal memory, assayed by memory scores. The skilled artisan would then be required to determine if this relationship existed in *any* population. Given the conflicting results in the specification and the art as to a predictable association between the valine and methionine allele and different disorders or cognitive affects in different populations, as well as the conflicting teachings of the art (e.g., see Egan 2003, addressed below in response to applicant's traversal citing Egan) such analysis would be replete with trial and error experimentation, the results of which are completely unpredictable. Given the teachings of the art that the affects of the allele appear to be influenced by the genetic background it is found in, the results of such analysis are completely unpredictable, as neither the specification, nor the art at the time of filing, teach how the allele is associated with the claimed phenotypes. It was not known whether the alleles themselves are functionally associated, or linked to some functionally associated alteration hundreds or thousands of nucleotides away. Additionally, given the teachings of the Goldsby, unpredictable trial and error experimentation would be required to practice the invention as broadly claimed with regard to protein analysis, additionally required for claims 13-14, 16-17, 19-20, 22-23.

Therefore, in light of the breadth of the claims, the conflicting guidance in the specification, the high level of unpredictability in the art as exemplified by the numerous studies which provide conflicting data regarding associations with val66met allele with various phenotypes, the nature of the invention, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to make or use the invention as broadly claimed.

### ***Response to Arguments***

10. The response traverses the rejection. With regard to verbal memory, the response asserts that the inventors examined the effects of the val/met polymorphism and that “the met allele was associated with impaired hippocampal verbal memory assayed with memory scores, hippocampal activation, assayed with fMRI and hippocampal NAA assayed with MRI”. The response provides analysis of applicant’s post filing date work, Egan 2003. However, the comments made in the response are attorney’s arguments and cannot take the place of evidence on the record. MPEP, 2106 notes “Arguments of Counsel”: “However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant’s attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement.” The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements

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or representations made are correct as provided by 35 U.S.C. 25 and 18, U.S.C. 1001. In *Ex parte Gray* (10 USPQ2d 1923) the Courts held that conclusory statements made in publications could not substitute for declaratory evidence filed under 37 CFR 1.132. Furthermore, in *Ex parte Ishizaka* (BdPatApp&Int 24 USPQ2d 1621), the Courts stated that 37 CFR 1.132 does not recognize the use of a publication as a substitute for a declaration. Consequently, a Declaration filed under 37 CFR 1.132 sworn by at least one of the instant inventors which cites/explains the relevant parts of the cited references is needed. This should not be construed as an invitation for providing evidence, As further stated in the MPEP 716.01:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In *re Rothermel*, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

- (1) prior to a final rejection,
- (2) before appeal in an application not having a final rejection, or
- (3) after final rejection and submitted
  - (i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
  - (ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
  - (iii) under 37 CFR 1.129(a).

The arguments in the response, as well as the Egan reference have been thoroughly reviewed but were not found persuasive to overcome the rejection. Firstly, although the specification teaches that “the rarer met allele was associated with poorer performance” for verbal memory, the specification is silent as to which memory test was used. Although Egan teaches a significant association with the met allele and the WMS-R test (Figure 1A, and cited in the response), Egan also teaches that BDNF genotype had no significant effect in either the normal subjects or the entire cohort on a second memory test which required recall of word lists, the CVLT test (page

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258, 2<sup>nd</sup> para of “Results” section). Accordingly, the association between the met allele and impaired verbal memory does not appear to be predictable. Secondly, the response cites numerous portions of post filing date work that lack nexus with the teachings in the specification. Notably, the specification is silent with regard to the different memory tests used in Egan et al, the sample size in the specification appears smaller than that cited in Egan et al, the specification is silent with regard to the statistical analysis with regard to homozygosity or heterozygosity of the met/val polymorphism in certain tests, and the specification is silent with regard to the ethnicities of the subjects assayed in the study. However, post filing date work cannot be used to supplement the disclosure in the specification. Additionally, although Egan teaches that demographic parameters were matched, the specification is silent as to this analysis, and both Egan and the specification do not provide analysis that takes into account different ethnic populations, although the post filing date art of Bath teaches is important. It is noted that the response also cites Bath as “showed recognition by others”, however Bath specifically addresses the unpredictability of the effect of the met/val polymorphism in different ethnicities. Bath teaches “It is still unclear what these findings mean for a broader population... the Met allele is not uniformly distributed across all ethnicities or all regions of the world... northern Europeans appear to be much more affected than Asian populations despite the fact that a higher proportion of the Asian population carries this [Met] allele.” At page 12, the response also asserts that Egan teaches that no affect of BDNF genotype was seen on other types of memory, such as semantic memory, however neither the specification nor Egan provide for a definition of “verbal memory” to exclude semantic memory, for example. Further, in referencing “hippocampal dependent verbal memory”, as the claims have been newly amended to recite, the response points to

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teachings in Egan 2003 which are not provided for in the specification. It is not clear how the specification provides support for this new claim amendment. Bath references the N-back test taught by Egan 2003 for suggestion as to hippocampal dependent memory, however the instant specification is silent as to which memory tests were used. Additionally, Egan 2003 states “these results suggest that the val66met polymorphism exerts its most robust effects on episodic memory” to which the specification is completely silent, nor would the skilled artisan be able to determine this conclusion based on the teachings in the specification. Further, the Egan et al 2001 (PNAS vol. 98, 6917) does not appear to supplement this lack of disclosure in the specification.

With regard to hippocampal function, the response again reference para 0008 of the specification, as well as the teachings of Egan 2003, and Bath, both post filing date works. The response asserts that “BDNF met/val subjects showed abnormal hippocampal activation during memory tasks and were significantly different compared to val/val subjects”. However, this sentence could not be found in the specification. The specification teaches “the met allele was also associated with reduced HIP NAA ( $p < 0.07$ )”, which does not appear to be statistically significant. Although the specification teaches that in two separate cohorts studied with fMRI, subjects with a met allele had abnormal patterns of hippocampal activation while performing memory tasks, the specification does not teach if this result was statistically significant.

Additionally, the specification notes that schizophrenia appears to involve hippocampal abnormalities, including reduced HIP NAA, a measure of neuronal integrity assessed with MRS. Egan 2003, however, teaches that BDNF genotype did not significantly affect right hippocampal NAA measures (page 260, col. 2).

The response then asserts that the level of skill in the art was high and that the methods needed to practice the invention were well known. The reference cites that with regard to verbal memory, Neuropsychological tests were known and cites Egan et al; (Biol Psychiatry, 50: 98; 2001) and Weickert et al; Arch. Gen. Psychiatry, 2000, vol. 57, and that fMRI was known in the art. These arguments have been thoroughly reviewed but were not found persuasive. These teachings reflect general teachings in the art, however they do not address the unpredictability reflected by numerous references cited above, with respect to association the BDNF met66val allele with different phenotypes and different ethnic populations. The met66val allele has been widely studied, and different groups have provided conflicting evidence of association with the same phenotype. Additionally, the post filing date work of Egan 2003 appears to provide conflicting evidence with regard to memory task which required recall of a list of words immediately after hearing the list in that no significant effects were observed with BDNF genotype. Additionally, Bath notes the unpredictability of the phenotypic effects of the BDNF genotype in different populations. The response asserts that Zhou et al; Neurochem, 91: 704, 2004 teaches that an antibody was produced that specifically recognizes the precursor BDNF and not mature BDNF and that methods of raising antibodies were well known in the art. This argument has been thoroughly reviewed but was not found persuasive. It is not questioned that an antibody can be raised to a particular protein, however the specificity of the antibody is dependent on specific epitopes. An antibody that can discriminate between the precursor BDNF and mature BDNF would not be capable of distinguishing between the val/met alleles. Thus, absent knowledge of the binding epitopes and the effects of the instant polymorphism on those

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epitopes, it is difficult to predict whether or not any generated antibody will be able to function to differentiate the two alleles in an assay.

***Conclusion***

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Jehanne Sitton  
Primary Examiner  
Art Unit 1634

3/9/07